IN THE DISTRICT COURT IN AND FOR BECKHAM COUNTY
STATE OF OKLAHOMA

STATE OF OKLAHOMA,	)	**Case No.: CF-2015-188**
	)	
Plaintiff,	)	
	)	
vs.	)	
	)	
KENNETH HAROLD TIBBETTS,	)	
	)	
Defendant.	)	

BECKHAM COUNTY FILED APR 18 2016 DONNA HOWELL, COURT CLERK BY ______ DEPUTY

BRIEF IN SUPPORT OF APPLICATION TO WITHDRAW PLEA OF GUILTY

COMES NOW the Defendant, by and through his counsel, Richard L. Yohn, Esq., of **Oklahoma Indigent Defense System**, and issues the following brief on behalf of the Defendant, and in support of his Application to Withdraw Plea of Guilty, to-wit:

1. The Defendant states to counsel that his has been diagnosed and suffered from hemochromatosis (accumulation of iron), cirrhosis of the liver (caused by the high iron levels), and hepatis C. The combination has various side effects as explained in the literature attached hereto.

2. One of the side effects of the combination is Hepatic Encephalopathy. This has a symptom of mental confusion, altered level of consciousness and can result in a coma.

3. The Defendant states that he was not in his correct mind when the incidents causing the current charges occurred and thus, was mental deficient when acting.

4. An expert is needed to correctly evaluate the possibility and likelihood of whether the Hepatic Encephalopathy could have and/or did cause the Defendant to be in an altered state of mind when the crimes occurred.

5. The state of mind at the time of the incident is crucial to a fair and impartial determination of guilt and what type of punishment, if any, should be issued.

6. Counsel has attached three articles found from Wikipedia, on-line, for the Court's information and review on the conditions that may have affected the Defendant when committing the crimes charged.

EXHIBIT 4

7. Defense counsel, not having a medical degree, is not able to evaluate or in the least way, determine whether the Defendant suffered from the infirmative and whether the infirmative affected his actions. Such determination would have to be made by a highly specialized expert dealing with the affects of medical conditions and their side affects on the working of the brain and process of information received.

WHEREFORE, the Defendant, by and through his counsel, prays this Court will consider all the information presented that is attached, reconsider the determination of the sentence and whether this Defendant is guilty of the crime, and allow a proper jury trial on the issues of guilt and punishment.

Respectfully submitted,

Richard L. Yohn, OBA# 14911
OKLAHOMA INDIGENT DEFENSE SYSTEM
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CERTIFICATE OF MAILING

I certify that a true and correct copy of the foregoing instrument was either hand delivered or mailed, U.S. Postage prepaid, on this 19th day of April, 2016, to:

District Attorney's Office
302 E. Main, Ste 302
Sayre, OK 73662

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Elk City, OK 73648

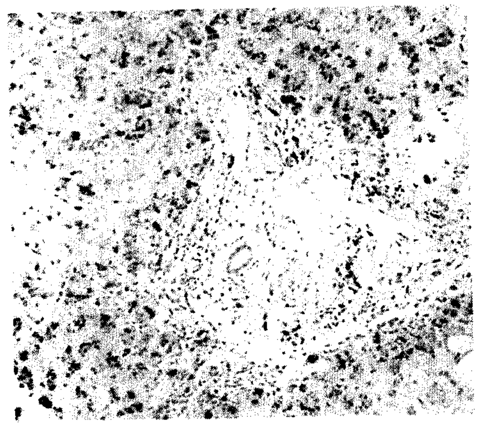
Richard L. Yohn, Esq.

Iron overload

From Wikipedia, the free encyclopedia

Iron overload, also known as **hemochromatosis** or **haemochromatosis**, indicates accumulation of iron in the body from any cause. The most important causes are hereditary haemochromatosis (HHC), a genetic disorder, and transfusional iron overload, which can result from repeated blood transfusions.[1][2]

Iron overload



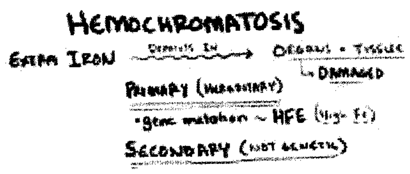
Micrograph of haemosiderosis. Liver biopsy. Iron stain.

Classification and external resources

Specialty	Hematology
ICD-10	R79.0 (http://apps.who.int/classifications/icd10/browse/2015/en#/R79.0)
ICD-9-CM	275.03 (http://www.icd9data.com/getICD9Code.ashx?icd9=275.03)
DiseasesDB	5581 (http://www.diseasesdatabase.com/ddb5581.htm)
MedlinePlus	000327 (http://www.nlm.nih.gov/medlineplus/ency/article/000327.htm)
MeSH	D019190 (https://www.nlm.nih.gov/cgi/mesh/2016/MB_cgi?field=uid&term=D019190)

Contents

Signs and symptoms



An explanation of hemochromatosis

Organs commonly affected by haemochromatosis are the liver, heart, and endocrine glands.[3]

Haemochromatosis may present with the following clinical syndromes:[4]

- Cirrhosis of the liver: Varies from zonal iron deposition[5] to fibrosis (cirrhosis).
- Diabetes due to selective iron deposition in pancreatic islet beta cells leading to functional failure and cell death.[2][6]
- Cardiomyopathy
- Arthritis (calcium pyrophosphate deposition in joints)
- Testicular failure
- Slate gray discoloration of the skin
- Diabetes
- Joint pain and bone pain[7]

Causes

The causes can be distinguished between primary cases (hereditary or genetically determined) and less frequent secondary cases (acquired during life).[8] People of Celtic (Irish, Scottish, Welsh, Cornish, Breton etc.), English, and Scandinavian origin[9] have a particularly high incidence of whom about 10% are carriers of the C282Y mutation on the HFE gene associated with HLA-A3 and 1% suffer from the condition.

Primary haemochromatosis

Although it was known most of the 20th century that most cases of haemochromatosis were inherited, they were incorrectly assumed to depend on a single gene.[10] The overwhelming majority depend on mutations of the HFE gene discovered in 1996, but since then others have been discovered and sometimes are grouped together as "non-classical hereditary haemochromatosis",[11] "non-HFE related hereditary haemochromatosis",[12] or "non-HFE haemochromatosis".[13]

Description	OMIM	Mutation
Haemochromatosis type 1: "classical" haemochromatosis	235200 (https://omim.org/entry/235200)	HFE
Haemochromatosis type 2A: juvenile haemochromatosis	602390 (https://omim.org/entry/602390)	Haemojuvelin ("HJV", also known as RGMc and HFE2)
Haemochromatosis type 2B: juvenile haemochromatosis	606464 (https://omim.org/entry/606464)	hepcidin antimicrobial peptide (*HAMP*) or HFE2B
Haemochromatosis type 3	604250 (https://omim.org/entry/604250)	transferrin receptor-2 (TFR2 or HFE3)
Haemochromatosis type 4/ African iron overload	604653 (https://omim.org/entry/604653)	ferroportin (SLC11A3/SLC40A1)
Neonatal haemochromatosis	231100 (https://omim.org/entry/231100)	(unknown)
Acaeruloplasminaemia (very rare)	604290 (https://omim.org/entry/604290)	caeruloplasmin
Congenital atransferrinaemia (very rare)	209300 (https://omim.org/entry/209300)	transferrin
GRACILE syndrome (very rare)	603358 (https://omim.org/entry/603358)	BCS1L

Most types of hereditary haemochromatosis have autosomal recessive inheritance, while type 4 has autosomal dominant inheritance.[14]

Secondary haemochromatosis

- Severe chronic haemolysis of any cause, including intravascular haemolysis and ineffective erythropoiesis (haemolysis within the bone marrow)
- Multiple frequent blood transfusions [2] (either whole blood or just red blood cells), which are usually needed either by individuals with hereditary anaemias (such as beta-thalassaemia major, sickle cell anaemia, and Diamond–Blackfan anaemia) or by older patients with severe acquired anaemias such as in myelodysplastic syndromes
- Excess parenteral iron supplements, such as what can acutely happen in iron poisoning
- Excess dietary iron
- Some disorders do not normally cause haemochromatosis on their own, but may do so in the presence of other predisposing factors. These include cirrhosis (especially related to alcohol abuse), steatohepatitis of any cause, porphyria cutanea tarda, prolonged haemodialysis, and post-portacaval shunting

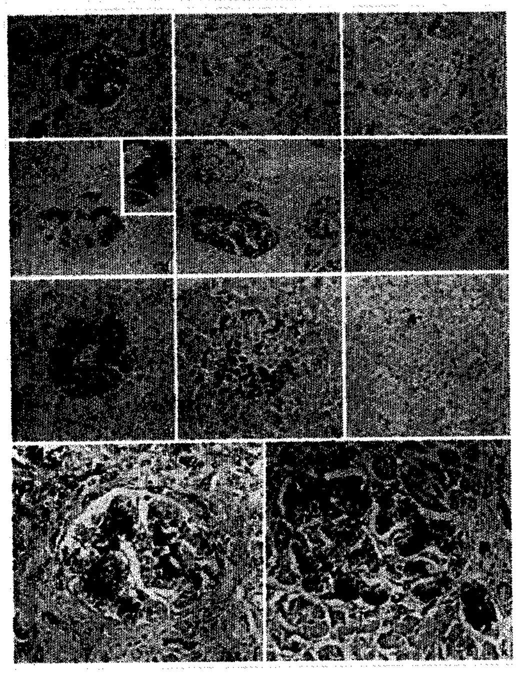
Diagnosis

There are several methods available for diagnosing and monitoring iron loading including:

- Serum ferritin

- Liver biopsy
- HFE
- MRI

Serum ferritin testing is a low-cost, readily available, and minimally invasive method for assessing body iron stores. However, the major problem with using it as an indicator of iron overload is that it can be elevated in a range of other medical conditions unrelated to iron levels including infection, inflammation, fever, liver disease, renal disease, and cancer. Also, total iron binding capacity may be low, but can also be normal.[15]



Selective iron deposition (blue) in pancreatic islet beta cells(red).

The standard of practice in diagnosis of haemochromatosis was recently reviewed by Pietrangelo.[16] Positive HFE analysis confirms the clinical diagnosis of haemochromatosis in asymptomatic individuals with blood tests showing increased iron stores, or for predictive testing of individuals with a family history of haemochromatosis. The alleles evaluated by HFE gene analysis are evident in ~80% of patients with haemochromatosis; a negative report for HFE gene does not rule out haemochromatosis. In a patient with negative HFE gene testing, elevated iron status for no other obvious reason, and family history of liver disease, additional evaluation of liver iron concentration is indicated. In this case, diagnosis of haemochromatosis is based on biochemical analysis and histologic examination of a liver biopsy. Assessment of the hepatic iron index (HII) is considered the "gold standard" for diagnosis of haemochromatosis.

Magnetic resonance imaging (MRI) is emerging as a noninvasive alternative to accurately estimate iron deposition levels in the liver as well as heart, joints, and pituitary gland.,[17][18][19][19]

Screening

Family members of those with primary haemochromatosis should be screened to determine if they are a carrier or if they could develop the disease. This can allow preventive measures to be taken.

Screening the general population is not recommended.[20]

Treatment

Routine treatment in an otherwise-healthy person consists of regularly scheduled phlebotomies (bloodletting). When first diagnosed, the phlebotomies may be fairly frequent, perhaps as often as once a week, until iron levels can be brought to within normal range. Once iron and other markers are within the normal range, phlebotomies may be scheduled every other month or every three months depending upon the patient's rate of iron loading. Each session typically draws from 450 to 500 cc.[21]

For those unable to tolerate routine blood draws, there is a chelating agent available for use.[22] The drug deferoxamine binds with iron in the bloodstream and enhances its elimination in urine and faeces. Typical treatment for chronic iron overload requires subcutaneous injection over a period of 8–12 hours daily. Two newer iron chelating drugs that are licensed for use in patients receiving regular blood transfusions to treat thalassaemia (and, thus, who develop iron overload as a result) are deferasirox and deferiprone.[23][24]

Prognosis

Affected individuals over age 40 or who have high serum ferritin levels are at risk for developing cirrhosis. Iron overload increases the risk of hepatocellular carcinoma.[25] This risk is greater in those with cirrhosis but is still present in those without cirrhosis.[25] Significant problems occur in around one in ten.[20]

Epidemiology

It is most common in certain European populations (such as the Irish and Norwegians) and occurs in 0.6% of the population.[20] Men with the disease are 24 times more likely to experience symptoms than affected women.[20]

Terminology

Historically, the term haemochromatosis (spelled hemochromatosis in American English) was initially used to refer to what is now more specifically called haemochromatosis type 1 (or HFE-related hereditary haemochromatosis). Currently, haemochromatosis (without further specification) is mostly defined as iron overload with a hereditary/primary cause,[26][27] or originating from a metabolic disorder.[28] However, the term is currently also used more broadly to refer to any form of iron overload, thus requiring specification of the cause, for example, *hereditary haemochromatosis*. Hereditary haemochromatosis is an autosomal recessive disorder with estimated prevalence in the population of 1 in 200 among patients with European ancestry, with lower incidence in other ethnic groups.[29] The gene responsible for hereditary haemochromatosis (known as HFE gene) is located on chromosome 6; the majority of hereditary haemochromatosis patients have mutations in this HFE gene.

Hereditary haemochromatosis is characterized by an accelerated rate of intestinal iron absorption and progressive iron deposition in various tissues. This typically begins to be expressed in the third to fifth decades of life, but may occur in children. The most common presentation is hepatic (liver) cirrhosis in combination with hypopituitarism, cardiomyopathy, diabetes, arthritis, or hyperpigmentation. Because of the severe sequelae of this disorder if left untreated, and recognizing that treatment is relatively simple, early diagnosis before symptoms or signs appear is important.[16][30]

In general, the term *haemosiderosis* is used to indicate the pathological effect of iron accumulation in any given organ, which mainly occurs in the form of the iron-storage complex haemosiderin.[31][32] Sometimes, the simpler term siderosis is used instead.

Other definitions distinguishing haemochromatosis or haemosiderosis that are occasionally used include:

- Haemosiderosis is haemochromatosis caused by excessive blood transfusions, that is, haemosiderosis is a form of secondary haemochromatosis.[33][34]
- Haemosiderosis is haemosiderin deposition within cells, while haemochromatosis is haemosiderin within cells and interstitium.[35]
- Haemosiderosis is iron overload that does not cause tissue damage,[36] while haemochromatosis does.[37]
- Haemosiderosis is arbitrarily differentiated from haemochromatosis by the reversible nature of the iron accumulation in the reticuloendothelial system.[38]

See also

- Human iron metabolism
- Iron deficiency

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Further reading

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External links

Wikimedia Commons has media related to ***Hemochromatosis***.

- Iron overload (https://www.dmoz.org/Health/Conditions_and_Diseases/Blood_Disorders/Hemochromatosis/) at DMOZ
- GeneReview/NCBI/NIH/UW entry on HFE-Associated Hereditary Hemochromatosis (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=hemochromatosis)
- GeneReview/NCBI/NIH/UW entry on TFR2-Related Hereditary Hemochromatosis (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=tfr2)
- GeneReview/NCBI/NIH/UW entry on Juvenile Hereditary Hemochromatosis (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=jh)
- GeneReview/NCBI/NIH/UW entry on Aceruloplasminemia (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=acp)

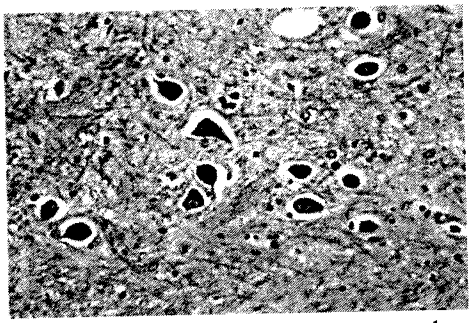
Categories: Inborn errors of metal metabolism | Abnormal clinical and laboratory findings for blood

Hepatic encephalopathy

From Wikipedia, the free encyclopedia

Hepatic encephalopathy (**HE**) is the occurrence of confusion, altered level of consciousness, and coma as a result of liver failure. In the advanced stages it is called **hepatic coma** or **coma hepaticum**. It may ultimately lead to death.[1]

Hepatic encephalopathy



Micrograph of Alzheimer type II astrocytes, as may be seen in hepatic encephalopathy.

Classification and external resources

Synonyms	portosystemic encephalopathy
Specialty	Gastroenterology
ICD-10	K72 (http://apps.who.int/classifications/icd10/browse/2015/en#/K72)
ICD-9-CM	572.2 (http://www.icd9data.com/getICD9Code.ashx?icd9=572.2)
MedlinePlus	000302 (http://www.nlm.nih.gov/medlineplus/ency/article/000302.htm)
eMedicine	med/3185 (http://www.emedicine.com/med/topic3185.htm) article/182208 (http://emedicine.medscape.com/article/182208-overview)
MeSH	D006501 (https://www.nlm.nih.gov/cgi/mesh/2016/MB_cgi?field=uid&term=D006501)

It is caused by accumulation in the bloodstream of toxic substances that are normally removed by the liver. The diagnosis of hepatic encephalopathy requires the presence of impaired liver function and the exclusion of an alternative explanation for the symptoms. Blood tests (ammonia levels) may assist in the diagnosis. Attacks are often cause by another problem, such as infection or constipation.[1][2]

Hepatic encephalopathy is reversible with treatment. This relies on suppressing the production of the toxic substances in the intestine and is most commonly done with the laxative lactulose or with non-absorbable antibiotics. In addition, the treatment of any underlying condition may improve the symptoms. In particular settings, such as acute liver failure, the onset of encephalopathy may indicate the need for a liver transplant.[1][3]

Contents

Signs and symptoms

The mildest form of hepatic encephalopathy is difficult to detect clinically, but may be demonstrated on neuropsychological testing. It is experienced as forgetfulness, mild confusion, and irritability. The first stage of hepatic encephalopathy is characterised by an inverted sleep-wake pattern (sleeping by day, being awake at night). The second stage is marked by lethargy and personality changes. The third stage is marked by worsened confusion. The fourth stage is marked by a progression to coma.[1]

More severe forms of hepatic encephalopathy lead to a worsening level of consciousness, from lethargy to somnolence and eventually coma. In the intermediate stages, a characteristic jerking movement of the limbs is observed (asterixis, "liver flap" due to its flapping character); this disappears as the somnolence worsens. There is disorientation and amnesia, and uninhibited behaviour may occur. In the third stage, neurological examination may reveal clonus and positive Babinski sign. Coma and seizures represent the most advanced stage; cerebral oedema (swelling of the brain tissue) leads to death.[1]

Encephalopathy often occurs together with other symptoms and signs of liver failure. These may include jaundice (yellow discolouration of the skin and the whites of the eyes), ascites (fluid accumulation in the abdominal cavity), and peripheral edema (swelling of the legs due to fluid build-up in the skin). The tendon reflexes may be exaggerated, and the plantar reflex may be abnormal, namely extending rather than flexing (Babinski's sign) in severe encephalopathy. A particular smell (*foetor hepaticus*) may be detected.[2]

Causes

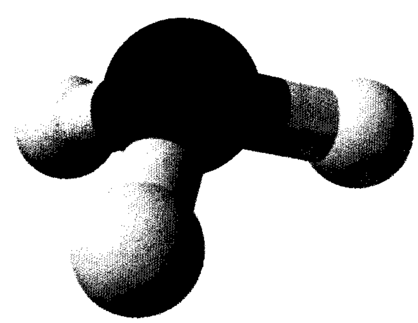
In a small proportion of cases, the encephalopathy is caused directly by liver failure; this is more likely in acute liver failure. More commonly, especially in chronic liver disease, hepatic encephalopathy is caused or aggravated by an additional cause, and identifying these causes can be important to treat the episode effectively.[1]

Type	Causes[1][2][4]
Excessive nitrogen load	Consumption of large amounts of protein, gastrointestinal bleeding e.g. from esophageal varices (blood is high in protein, which is reabsorbed from the bowel), renal failure (inability to excrete nitrogen-containing waste products such as urea), constipation
Electrolyte or metabolic disturbance	Hyponatraemia (low sodium level in the blood) and hypokalaemia (low potassium levels)—these are both common in those taking diuretics, often used for the treatment of ascites; furthermore alkalosis (decreased acid level), hypoxia (insufficient oxygen levels), dehydration
Drugs and medications	Sedatives such as benzodiazepines (often used to suppress alcohol withdrawal or anxiety disorder), narcotics (used as painkillers or drugs of abuse) and sedative antipsychotics, alcohol intoxication
Infection	Pneumonia, urinary tract infection, spontaneous bacterial peritonitis, other infections
Others	Surgery, progression of the liver disease, additional cause for liver damage (e.g. alcoholic hepatitis, hepatitis A)
Unknown	In 20–30% of cases, no clear cause for an attack can be found

Hepatic encephalopathy may also occur after the creation of a transjugular intrahepatic portosystemic shunt (TIPSS). This is used in the treatment of refractory ascites, bleeding from oesophageal varices and hepatorenal syndrome.[5][6] TIPSS-related encephalopathy occurs in about 30% of cases, with the risk being higher in those with previous episodes of encephalopathy, higher age, female sex and liver disease due to causes other than alcohol.[4]

Pathogenesis

There are various explanations why liver dysfunction or portosystemic shunting might lead to encephalopathy. In healthy subjects, nitrogen-containing compounds from the intestine, generated by gut bacteria from food, are transported by the portal vein to the liver, where 80–90% are metabolised through the urea cycle and/or excreted immediately. This process is impaired in all subtypes of hepatic encephalopathy, either because the hepatocytes (liver cells) are incapable of metabolising the waste products or because portal venous blood bypasses the liver through collateral circulation or a medically constructed shunt. Nitrogenous waste products accumulate in the systemic circulation (hence the older term "portosystemic encephalopathy"). The most important waste product is ammonia (NH_3). This small molecule crosses the blood–brain barrier and is absorbed and metabolised by the astrocytes, a population of



Ball and stick model of ammonia; one nitrogen atom with three hydrogen atoms. Accumulation of ammonia in the bloodstream is associated with hepatic encephalopathy.

cells in the brain that constitutes 30% of the cerebral cortex. Astrocytes use ammonia when synthesising glutamine from glutamate. The increased levels of glutamine lead to an increase in osmotic pressure in the astrocytes, which become swollen. There is increased activity of the inhibitory γ-aminobutyric acid (GABA) system, and the energy supply to other brain cells is decreased. This can be thought of as an example of brain oedema of the "cytotoxic" type.[7]

Despite numerous studies demonstrating the central role of ammonia, ammonia levels don't always correlate with the severity of the encephalopathy; it is suspected that this means that more ammonia has already been absorbed into the brain in those with severe symptoms whose serum levels are relatively low.[1][2] Other waste products implicated in hepatic encephalopathy include mercaptans (substances containing a thiol group), short-chain fatty acids and phenol.[2]

Numerous other abnormalities have been described in hepatic encephalopathy, although their relative contribution to the disease state is uncertain. Loss of glutamate transporter gene expression (especially EAAT 2) has been attributed to acute liver failure.[8] Benzodiazepine-like compounds have been detected at increased levels as well as abnormalities in the GABA neurotransmission system. An imbalance between aromatic amino acids (phenylalanine, tryptophan and tyrosine) and branched-chain amino acids (leucine, isoleucine and valine) has been described; this would lead to the generation of false neurotransmitters (such octopamine and 2-hydroxyphenethylamine). Dysregulation of the serotonin system, too, has been reported. Depletion of zinc and accumulation of manganese may play a role.[1][2] Inflammation elsewhere in the body may precipitate encephalopathy through the action of cytokines and bacterial lipopolysaccharide on astrocytes.[4]

Diagnosis

Investigations

The diagnosis of hepatic encephalopathy can only be made in the presence of confirmed liver disease (types A and C) or a portosystemic shunt (type B), as its symptoms are similar to those encountered in other encephalopathies. To make the distinction, abnormal liver function tests and/or ultrasound suggesting liver disease are required, and ideally liver biopsy.[1][2] The symptoms of hepatic encephalopathy may also arise from other conditions, such as cerebral haemorrhage and seizures (both of which are more common in chronic liver disease). A CT scan of the brain may be required to exclude haemorrhage, and if seizure activity is suspected an electroencephalograph (EEG) study may be performed.[1] Rarer mimics of encephalopathy are meningitis, encephalitis, Wernicke's encephalopathy and Wilson's disease; these may be suspected on clinical grounds and confirmed with investigations.[2][9]

The diagnosis of hepatic encephalopathy is a clinical one, once other causes for confusion or coma have been excluded; no test fully diagnoses or excludes it. Serum ammonia levels are elevated in 90% of patients, but not all hyperammonaemia (high ammonia levels) is associated with encephalopathy.[1][2] A CT scan of the brain usually shows no abnormality except in stage IV encephalopathy, when cerebral oedema may be visible.[2] Other neuroimaging modalities, such as magnetic resonance imaging (MRI), are not currently regarded as useful, although they may show abnormalities.[9] Electroencephalography shows no clear abnormalities in stage 0, even if minimal HE is present; in stages I, II and III there are

triphasic waves over the frontal lobes that oscillate at 5 Hz, and in stage IV there is slow delta wave activity.[1] However, the changes in EEG are not typical enough to be useful in distinguishing hepatic encephalopathy from other conditions.[9]

Once the diagnosis of encephalopathy has been made, efforts are made to exclude underlying causes (such as listed above in "causes"). This requires blood tests (urea and electrolytes, full blood count, liver function tests), usually a chest X-ray, and urinalysis. If there is ascites, diagnostic paracentesis (removal of a fluid sample with a needle) may be required to identify spontaneous bacterial peritonitis (SBP).[1]

Micrograph of Alzheimer type II astrocytes, as may be seen in hepatic encephalopathy.

Classification

West Haven criteria

The severity of hepatic encephalopathy is graded with the West Haven Criteria; this is based on the level of impairment of autonomy, changes in consciousness, intellectual function, behavior, and the dependence on therapy.[1][9]

- Grade 1 - Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
- Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behaviour
- Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation
- Grade 4 - Coma

Types

A classification of hepatic encephalopathy was introduced at the World Congress of Gastroenterology 1998 in Vienna. According to this classification, hepatic encephalopathy is subdivided in type A, B and C depending on the underlying cause.[9]

Micrograph showing liver cirrhosis, a condition that often precedes hepatic encephalopathy. Trichrome stain.

- *Type A (=acute)* describes hepatic encephalopathy associated with acute liver failure, typically associated with cerebral oedema
- *Type B (=bypass)* is caused by portal-systemic shunting without associated intrinsic liver disease
- *Type C (=cirrhosis*) occurs in patients with cirrhosis - this type is subdivided in *episodic*, *persistent* and *minimal* encephalopathy

The term *minimal encephalopathy* (MHE) is defined as encephalopathy that does not lead to clinically overt cognitive dysfunction, but can be demonstrated with neuropsychological studies.[9][10] This is still an important finding, as minimal encephalopathy has been demonstrated to impair quality of life and increase the risk of involvement in road traffic accidents.[11]

Minimal HE

The diagnosis of minimal hepatic encephalopathy requires neuropsychological testing by definition. Older tests include the "numbers connecting test" A and B (measuring the speed at which one could connect randomly dispersed numbers 1–20), the "block design test" and the "digit-symbol test".[9] In 2009 an expert panel concluded that neuropsychological test batteries aimed at measuring multiple domains of cognitive function are generally more reliable than single tests, and tend to be more strongly correlated with functional status. Both the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[12] and PSE-Syndrom-Test[13] may be used for this purpose.[10] The PSE-Syndrom-Test, developed in Germany and validated in several other European countries, incorporates older assessment tools such as the number connection test.[9][10][11][13]

Treatment

Those with severe encephalopathy (stages 3 and 4) are at risk of obstructing their airway due to decreased protective reflexes such as the gag reflex. This can lead to respiratory arrest. Transferring the patient to a higher level of nursing care, such as an intensive care unit, is required and intubation of the airway is often necessary to prevent life-threatening complications (e.g., aspiration or respiratory failure).[2][3] Placement of a nasogastric tube permits the safe administration of nutrients and medication.[1]

The treatment of hepatic encephalopathy depends on the suspected underlying cause (types A, B or C) and the presence or absence of underlying causes. If encephalopathy develops in acute liver failure (type A), even in a mild form (grade 1–2), it indicates that a liver transplant may be required, and transfer to a specialist centre is advised.[3] Hepatic encephalopathy type B may arise in those who have undergone a TIPSS procedure; in most cases this resolves spontaneously or with the medical treatments discussed below, but in a small proportion of about 5%, occlusion of the shunt is required to address the symptoms.[4]

In hepatic encephalopathy type C, the identification and treatment of alternative or underlying causes is central to the initial management.[1][2][4][11] Given the frequency of infection as the underlying cause, antibiotics are often administered empirically (without knowledge of the exact source and nature of the infection).[1][4] Once an episode of encephalopathy has been effectively treated, a decision may need to be made on whether to prepare for a liver transplant.[11]

Diet

In the past, it was thought that consumption of protein even at normal levels increased the risk of hepatic encephalopathy. This has been shown to be incorrect. Furthermore, many people with chronic liver disease are malnourished and require adequate protein to maintain a stable body weight. A diet with adequate protein and energy is therefore recommended.[1][4]

Dietary supplementation with Branched-chain amino acids has shown improvement of encephalopathy and other complications of cirrhosis.[1][4] Some studies have shown benefit of administration of probiotics ("healthy bacteria").[4]

Lactulose/lactitol

Lactulose and lactitol are disaccharides that are not absorbed from the digestive tract. They are thought to decrease the generation of ammonia by bacteria, render the ammonia inabsorbable by converting it to ammonium (NH_4^+) ions, and increase transit of bowel content through the gut. Doses of 15-30 ml are administered three times a day; the result is aimed to be 3–5 soft stools a day, or (in some settings) a stool pH of <6.0.[1][2][4][11] Lactulose may also be given by enema, especially if encephalopathy is severe.[11] More commonly, phosphate enemas are used. This may relieve constipation, one of the causes of encephalopathy, and increase bowel transit.[1]

A 2004 review by the Cochrane Collaboration concluded that there was insufficient evidence to determine whether lactulose and lactitol are of benefit for hepatic encephalopathy,[14] but it remains the first-line treatment for type C hepatic encephalopathy.[1] In acute liver failure, it is unclear whether lactulose is beneficial. Furthermore, it may lead to bloating and as such interfere with a liver transplant procedure if required.[3]

Antibiotics

The antibiotic rifaximin is typically recommended. It is a nonabsorbable antibiotic from the rifamycin class. This is thought to work in a similar way to other antibiotics, but without the complications attached to neomycin and metronidazole. The use of rifaximin is supported by better evidence than lactulose.[14] Due to the long history and lower cost of lactulose use, rifaximin is only used as a second-line treatment if lactulose is poorly tolerated or not effective. When rifaximin is added to lactulose, the combination of the two may be more effective than each component separately.[1] Rifaximin is more expensive than lactulose, but the cost may be offset by reduced hospital admissions for encephalopathy.[11]

The antibiotics neomycin and metronidazole were previously used as a treatment for hepatic encephalopathy. The rationale of their use was the fact that ammonia and other waste products are generated and converted by intestinal bacteria, and killing these bacteria would reduce the generation of these waste products. Neomycin was chosen because of its low intestinal absorption, as neomycin and similar aminoglycoside antibiotics may cause hearing loss and renal failure if used parenterally. Later

studies showed that neomycin was indeed absorbed enterally, with resultant complications. Metronidazole, similarly, was abandoned because prolonged use could cause peripheral neuropathy (nerve damage), in addition to gastrointestinal side effects.[1]

LOLA

A preparation of *L*-ornithine and *L*-aspartate (LOLA) is used to increase the generation of urea through the urea cycle, a metabolic pathway that removes ammonia by turning it into the neutral substance urea. It may be combined with lactulose and/or rifaximin if these alone are ineffective at controlling symptoms.[1]

Epidemiology and prognosis

In those with cirrhosis, the risk of developing hepatic encephalopathy is 20% per year, and at any time about 30–45% of people with cirrhosis exhibit evidence of overt encephalopathy. The prevalence of minimal hepatic encephalopathy detectable on formal neuropsychological testing is 60–80%; this increases the likelihood of developing overt encephalopathy in the future.[11] Once hepatic encephalopathy has developed, the prognosis is determined largely by other markers of liver failure, such as the levels of albumin (a protein produced by the liver), the prothrombin time (a test of coagulation, which relies on proteins produced in the liver), the presence of ascites and the level of bilirubin (a breakdown product of hemoglobin which is conjugated and excreted by the liver). Together with the severity of encephalopathy, these markers have been incorporated into the Child-Pugh score; this score determines the one- and two-year survival and may assist in a decision to offer liver transplantation.[9]

In acute liver failure, the development of severe encephalopathy strongly predicts short-term mortality, and is almost as important as the nature of the underlying cause of the liver failure in determining the prognosis. Historically, widely used criteria for offering liver transplantation, such as King's College Criteria, are of limited use and recent guidelines discourage excessive reliance on these criteria. The occurrence of hepatic encephalopathy in patients with Wilson's disease (hereditary copper accumulation) and mushroom poisoning indicates an urgent need for a liver transplant.[3]

History

The occurrence of disturbed behaviour in people with jaundice may have been described in antiquity by Hippocrates of Cos (ca. 460–370 BCE).[13][15] Celsus and Galen (first and third century respectively) both recognised the condition. Many modern descriptions of the link between liver disease and neuropsychiatric symptoms were made in the eighteenth and nineteenth century; for instance, Giovanni Battista Morgagni (1682–1771) reported in 1761 that it was a progressive condition.[15]

In the 1950s, several reports enumerated the numerous abnormalities reported previously, and confirmed the previously enunciated theory that metabolic impairment and portosystemic shunting are the underlying mechanism behind hepatic encephalopathy, and that the nitrogen-rich compounds originate

from the intestine.[13][16] Many of these studies were done by Professor Dame Sheila Sherlock (1918–2001), then at the Royal Postgraduate Medical School in London and subsequently at the Royal Free Hospital. The same group investigated protein restriction[15] and neomycin.[17]

The West Haven classification was formulated by Prof Harold Conn (1925–2011) and colleagues at Yale University while investigating the therapeutic efficacy of lactulose.[9][18][19]

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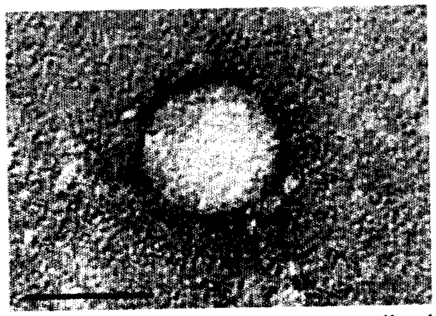
Categories: Diseases of liver | Hepatology | Brain disorders | Coma

Hepatitis C

From Wikipedia, the free encyclopedia

Hepatitis C is an infectious disease caused by the hepatitis C virus (HCV) that primarily affects the liver.[1] During the initial infection people often have mild or no symptoms. Occasionally a fever, dark urine, abdominal pain, and yellow tinged skin occurs. The virus persists in the liver in about 75% to 85% of those initially infected. Early on chronic infection typically has no symptoms. Over many years however, it often leads to liver disease and occasionally cirrhosis.[2] In some cases, those with cirrhosis will develop complications such as liver failure, liver cancer, or esophageal and gastric varices.[1]

Hepatitis C



Electron micrograph of hepatitis C virus from cell culture (scale = 50 nanometers)

Classification and external resources

Specialty	Gastroenterology, infectious disease
ICD-10	B17.1 (http://apps.who.int/classifications/icd10/browse/2015/en#/B17.1), B18.2 (http://apps.who.int/classifications/icd10/browse/2015/en#/B18.2)
ICD-9-CM	070.70 (http://www.icd9data.com/getICD9Code.ashx?icd9=070.70),070.4 (http://www.icd9data.com/getICD9Code.ashx?icd9=070.4), 070.5 (http://www.icd9data.com/getICD9Code.ashx?icd9=070.5)
OMIM	609532 (http://omim.org/entry/609532)
DiseasesDB	5783 (http://www.diseasesdatabase.com/ddb5783.htm)
MedlinePlus	000284 (http://www.nlm.nih.gov/medlineplus/ency/article/000284.htm)
eMedicine	med/993 (http://www.emedicine.com/med/topic993.htm) ped/979 (http://www.emedicine.com/ped/topic979.htm#)
Patient UK	Hepatitis C (http://patient.info/doctor/hepatitis-c-pro)
MeSH	D006526 (https://www.nlm.nih.gov/cgi/mesh/2016/MB_cgi?field=uid&term=D006526)

HCV is spread primarily by blood-to-blood contact associated with intravenous drug use, poorly sterilized medical equipment, needlestick injuries in healthcare, and transfusions.[2][3] With blood screening the risk from a transfusion is less than one per two million.[2] It may also be spread from an infected mother to her baby during birth.[2] It is not spread by superficial contact.[4] It is one of five known hepatitis viruses: A, B, C, D, and E.[5] Diagnosis is by blood testing to look for either antibodies to the virus or its RNA. Testing is recommended in all people who are at risk.[2]

There is no vaccine against hepatitis C.[2] Prevention includes harm reduction efforts among people who use intravenous drugs and testing donated blood.[4] Chronic infection can be cured about 90% of the time with treatments that include the medications sofosbuvir or simeprevir.[2][4] Previous to this a combination of peginterferon and ribavirin was used which had a cure rate around 50% and greater side effects. Getting access to

the newer treatments however can be expensive.[4] Those who develop cirrhosis or liver cancer may require a liver transplant. Hepatitis C is the leading reason for liver transplantation, though the virus usually recurs after transplantation.[6]

An estimated 130–200 million people worldwide are infected with hepatitis C.[4][7][8] In 2013 about 11 million new cases occurred.[9] It occurs most commonly in Africa and Central and East Asia.[4] About 343,000 deaths due to liver cancer and 358,000 deaths due to cirrhosis occurred in 2013 due to hepatitis C.[10] The existence of hepatitis C – originally identifiable only as a type of non-A non-B hepatitis – was suggested in the 1970s and proven in 1989.[11] Hepatitis C infects only humans and chimpanzees.[12]

Contents

Signs and symptoms

Acute infection

Hepatitis C infection causes acute symptoms in 15% of cases.[13] Symptoms are generally mild and vague, including a decreased appetite, fatigue, nausea, muscle or joint pains, and weight loss[14] and rarely does acute liver failure result.[15] Most cases of acute infection are not associated with jaundice.[16] The infection resolves spontaneously in 10–50% of cases, which occurs more frequently in individuals who are young and female.[16]

Chronic infection

About 80% of those exposed to the virus develop a chronic infection.[17] This is defined as the presence of detectable viral replication for at least six months. Most experience minimal or no symptoms during the initial few decades of the infection.[18] Chronic hepatitis C can be associated with fatigue[19] and mild cognitive problems.[20] Chronic infection after several years may cause cirrhosis or liver cancer.[6] The liver enzymes are normal in 7–53%.[21] Late relapses after apparent cure have been reported, but these can be difficult to distinguish from reinfection.[21]

Fatty changes to the liver occur in about half of those infected and are usually present before cirrhosis develops.[22][23] Usually (80% of the time) this change affects less than a third of the liver.[22] Worldwide hepatitis C is the cause of 27% of cirrhosis cases and 25% of hepatocellular carcinoma.[24] About 10–30% of those infected develop cirrhosis over 30 years.[6][14] Cirrhosis is more common in those also infected with hepatitis B, schistosoma, or HIV, in alcoholics and in those of male gender.[14] In those with hepatitis C, excess alcohol increases the risk of developing cirrhosis 100-fold.[25] Those who develop cirrhosis have a 20-fold greater risk of hepatocellular carcinoma. This transformation occurs at a rate of 1–3% per year.[6][14] Being infected with hepatitis B in addition to hepatitis C increases this risk further.[26]

Liver cirrhosis may lead to portal hypertension, ascites (accumulation of fluid in the abdomen), easy bruising or bleeding, varices (enlarged veins, especially in the stomach and esophagus), jaundice, and a syndrome of cognitive impairment known as hepatic encephalopathy.[27] Ascites occurs at some stage in more than half of those who have a chronic infection.[28]

Extrahepatic complications

The most common problem due to hepatitis C but not involving the liver is mixed cryoglobulinemia (usually the type II form) — an inflammation of small and medium-sized blood vessels.[29][30] Hepatitis C is also associated with the autoimmune disorder Sjögren's syndrome, a low platelet count, lichen planus, porphyria cutanea tarda, necrolytic acral erythema, insulin resistance, diabetes mellitus, diabetic nephropathy, autoimmune thyroiditis, and B-cell lymphoproliferative disorders.[31][32] 20–30% of people infected have rheumatoid factor — a type of antibody.[33] Possible associations include Hyde's prurigo nodularis[34] and membranoproliferative glomerulonephritis.[19] Cardiomyopathy with associated abnormal heart rhythms has also been reported.[35] A variety of central nervous system disorders has been reported.[36] Chronic infection seems to be associated with an increased risk of pancreatic cancer.[37]

Occult infection

Persons who have been infected with hepatitis C may appear to clear the virus but remain infected.[38] The virus is not detectable with conventional testing but can be found with ultra-sensitive tests.[39] The original method of detection was by demonstrating the viral genome within liver biopsies, but newer methods include an antibody test for the virus' core protein and the detection of the viral genome after first concentrating the viral particles by ultracentrifugation.[40] A form of infection with persistently moderately elevated serum liver enzymes but without antibodies to hepatitis C has also been reported.[41] This form is known as cryptogenic occult infection.

Several clinical pictures have been associated with this type of infection.[42] It may be found in people with anti-hepatitis-C antibodies but with normal serum levels of liver enzymes; in antibody-negative people with ongoing elevated liver enzymes of unknown cause; in healthy populations without evidence of liver disease; and in groups at risk for HCV infection including those on hemodialysis or family members of people with occult HCV. The clinical relevance of this form of infection is under investigation.[43] The consequences of occult infection appear to be less severe than with chronic infection but can vary from minimal to hepatocellular carcinoma.[40]

The rate of occult infection in those apparently cured is controversial but appears to be low.[21] 40% of those with hepatitis but with both negative hepatitis C serology and the absence of detectable viral genome in the serum have hepatitis C virus in the liver on biopsy.[44] How commonly this occurs in children is unknown.[45]

Virology

The hepatitis C virus (HCV) is a small, enveloped, single-stranded, positive-sense RNA virus.[6] It is a member of the *Hepacivirus* genus in the family *Flaviviridae*.[19] There are seven major genotypes of HCV, which are known as genotypes one to seven.[46] The genotypes are divided into several subtypes with the number of subtypes depending on the genotype. In the United States, about 70% of cases are caused by genotype 1, 20% by genotype 2 and about 1% by each of the other genotypes.[14] Genotype 1 is also the most common in South America and Europe.[6]

The half life of the virus particles in the serum is around 3 hours and may be as short as 45 minutes.[47][48] In an infected person, about 10^{12} virus particles are produced each day.[47] In addition to replicating in the liver the virus can multiply in lymphocytes.[49]

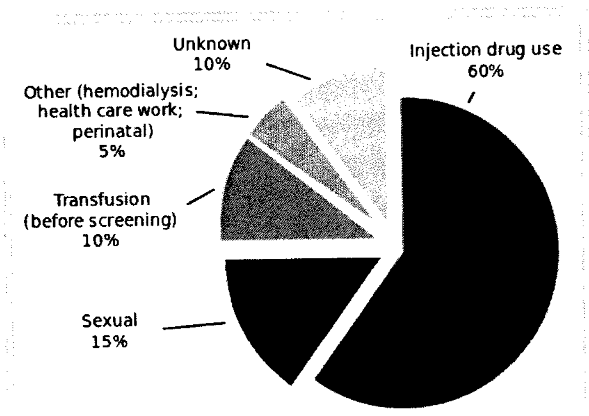
Transmission

The primary route of transmission in the developed world is intravenous drug use (IDU), while in the developing world the main methods are blood transfusions and unsafe medical procedures.[3] The cause of transmission remains unknown in 20% of cases;[50] however, many of these are believed to be accounted for by IDU.[16]

Drug use

Intravenous drug use (IDU) is a major risk factor for hepatitis C in many parts of the world.[51] Of 77 countries reviewed, 25 (including the United States) were found to have prevalences of hepatitis C in the intravenous drug user population of between 60% and 80%.[17][51] Twelve countries had rates greater than 80%.[17] It is believed

that ten million intravenous drug users are infected with hepatitis C; China (1.6 million), the United States (1.5 million), and Russia (1.3 million) have the highest absolute totals.[17] Occurrence of hepatitis C among prison inmates in the United States is 10 to 20 times that of the occurrence observed in the general population; this has been attributed to high-risk behavior in prisons such as IDU and tattooing with nonsterile equipment.[52][53] Intranasal drug use may also be a risk factor.[54]



Hepatitis C infection in the United States by source

Healthcare exposure

Blood transfusion, transfusion of blood products, or organ transplants without HCV screening carry significant risks of infection.[14] The United States instituted universal screening in 1992[55] and Canada instituted universal screening in 1990.[56] This decreased the risk from one in 200 units[55] to between one in 10,000 to one in 10,000,000 per unit of blood.[16][50] This low risk remains as there is a period of about 11–70 days between the potential blood donor's acquiring hepatitis C and the blood's testing positive depending on the method.[50] Some countries do not screen for hepatitis C due to the cost.[24]

Those who have experienced a needle stick injury from someone who was HCV positive have about a 1.8% chance of subsequently contracting the disease themselves.[14] The risk is greater if the needle in question is hollow and the puncture wound is deep.[24] There is a risk from mucosal exposures to blood; but this risk is low, and there is no risk if blood exposure occurs on intact skin.[24]

Hospital equipment has also been documented as a method of transmission of hepatitis C, including reuse of needles and syringes; multiple-use medication vials; infusion bags; and improperly sterilized surgical equipment, among others.[24] Limitations in the implementation and enforcement of stringent standard precautions in public and private medical and dental facilities are known to be the primary cause of the spread of HCV in Egypt, the country with highest rate of infection in the world.[57]

Sexual intercourse

Whether hepatitis C can be transmitted through sexual activity is controversial.[58] While there is an association between high-risk sexual activity and hepatitis C, and multiple sexual partners are a risk factor for hepatitis C, there is no conclusive evidence that hepatitis C can be transmitted by sexual activity, since people who report transmission with sex as their only risk factor may actually have used drugs but denied it.[14] The majority of evidence supports there being no risk for heterosexual couples with only one sexual partner.[58] Sexual practices that involve higher levels of trauma to the anogenital mucosa, such as anal penetrative sex, or that occur when there is a concurrent sexually transmitted infection, including HIV or genital ulceration, do present a risk.[58] The United States Department of Veterans Affairs recommends condom use to prevent hepatitis C transmission in those with multiple partners, but not those in relationships that involve only a single partner.[59]

Body modification

Tattooing is associated with two to threefold increased risk of hepatitis C.[60] This can be due to either improperly sterilized equipment or contamination of the dyes being used.[60] Tattoos or piercings performed either before the mid-1980s, "underground," or nonprofessionally are of particular concern, since sterile techniques in such settings may be lacking. The risk also appears to be greater for larger tattoos.[60] It is estimated that nearly half of prison inmates share unsterilized tattooing equipment.[60] It is rare for tattoos in a licensed facility to be directly associated with HCV infection.[61]

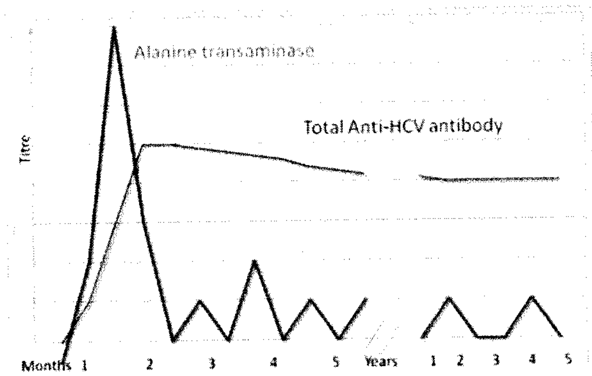
Shared personal items

Personal-care items such as razors, toothbrushes, and manicuring or pedicuring equipment can be contaminated with blood. Sharing such items can potentially lead to exposure to HCV.[62][63] Appropriate caution should be taken regarding any medical condition that results in bleeding, such as cuts and sores.[63] HCV is not spread through casual contact, such as hugging, kissing, or sharing eating or cooking utensils.[63] Neither is it transmitted through food or water.[64]

Vertical transmission

Vertical transmission of hepatitis C from an infected mother to her child occurs in less than 10% of pregnancies.[65] There are no measures that alter this risk.[65] It is not clear when transmission occurs during pregnancy, but it may occur both during gestation and at delivery.[50] A long labor is associated with a greater risk of transmission.[24] There is no evidence that breast-feeding spreads HCV; however, to be cautious, an infected mother is advised to avoid breastfeeding if her nipples are cracked and bleeding,[66] or if her viral loads are high.[50]

Diagnosis



Serologic profile of Hepatitis C infection

There are a number of diagnostic tests for hepatitis C, including HCV antibody enzyme immunoassay or ELISA, recombinant immunoblot assay, and quantitative HCV RNA polymerase chain reaction (PCR).[14] HCV RNA can be detected by PCR typically one to two weeks after infection, while antibodies can take substantially longer to form and thus be detected.[27]

Chronic hepatitis C is defined as infection with the hepatitis C virus persisting for more than six months based on the presence of its RNA.[18] Chronic infections are typically asymptomatic during the first few decades,[18] and thus are most commonly discovered following the investigation of elevated liver enzyme levels or during a routine screening of high-risk individuals. Testing is not able to distinguish between acute and chronic infections.[24] Diagnosis in the infant is difficult as maternal antibodies may persist for up to 18 months.[45]

Serology

Hepatitis C testing typically begins with blood testing to detect the presence of antibodies to the HCV, using an enzyme immunoassay.[14] If this test is positive, a confirmatory test is then performed to verify the immunoassay and to determine the viral load.[14] A recombinant immunoblot assay is used to verify the immunoassay and the viral load is determined by a HCV RNA polymerase chain reaction.[14] If there is no RNA and the immunoblot is positive, it means that the person tested had a previous infection but cleared it either with treatment or spontaneously; if the immunoblot is negative, it means that the immunoassay was wrong.[14] It takes about 6–8 weeks following infection before the immunoassay will test positive.[19] A number of tests are available as point of care testing which means that results are available within 30 minutes.[67]

Liver enzymes are variable during the initial part of the infection[18] and on average begin to rise at seven weeks after infection.[19] The elevation of liver enzymes does not closely follow disease severity.[19]

Biopsy

Liver biopsies are used to determine the degree of liver damage present; however, there are risks from the procedure.[6] The typical changes seen are lymphocytes within the parenchyma, lymphoid follicles in portal triad, and changes to the bile ducts.[6] There are a number of blood tests available that try to determine the degree of hepatic fibrosis and alleviate the need for biopsy.[6]

Screening

It is believed that only 5–50% of those infected in the United States and Canada are aware of their status.[60] Testing is recommended for those at high risk, which includes injection drug users, those who have received blood transfusions before 1992,[68] those who have been in jail, those on long term hemodialysis,[69] and those with tattoos.[60] Screening is also recommended in those with elevated liver enzymes, as this is frequently the only sign of chronic hepatitis.[70] Routine screening is not currently recommended in the United States.[14] In 2012, the U.S. Centers for Disease Control and Prevention (CDC) added a recommendation for a single screening test for those born between 1945 and 1965.[71]

Prevention

As of 2016, no approved vaccine protects against contracting hepatitis C.[72] However, there are a number of vaccines under development and some have shown encouraging results.[72]

A combination of harm reduction strategies, such as the provision of new needles and syringes and treatment of substance use, decreases the risk of hepatitis C in intravenous drug users by about 75%.[73] The screening of blood donors is important at a national level, as is adhering to universal precautions within healthcare facilities.[19] In countries where there is an insufficient supply of sterile syringes, medications should be given orally rather than via injection (when possible).[24]

Treatment

HCV induces chronic infection in 50–80% of infected persons. Approximately 40–80% of these clear with treatment.[74][75] In rare cases, infection can clear without treatment.[16] Those with chronic hepatitis C are advised to avoid alcohol and medications toxic to the liver,[14] and to be vaccinated for hepatitis A and hepatitis B.[14] Ultrasound surveillance for hepatocellular carcinoma is recommended in those with accompanying cirrhosis.[14]

Medications

Treatment with antiviral medication is recommended in all people with proven chronic hepatitis C who are not at high risk of dying from other causes.[76] People with the highest complication risk should be treated first, with the risk of complications based on the degree of liver scarring.[76] The initial recommended treatment depends on the type of hepatitis C virus with which a person is infected.[76]

- HCV genotype 1a: 12 weeks of ledipasvir and sofosbuvir OR 12 to 24 weeks of paritaprevir, ombitasvir, dasabuvir, and ribavirin[76]
- HCV genotype 1b: 12 weeks of ledipasvir and sofosbuvir OR 12 weeks of paritaprevir, ombitasvir, and dasabuvir[76]
- HCV genotype 2: 12 to 16 weeks of sofosbuvir and ribavirin[76]
- HCV genotype 3: 12 weeks of sofosbuvir, ribavirin, and pegylated interferon[76]
- HCV genotype 4: 12 weeks of ledipasvir and sofosbuvir OR paritaprevir, ritonavir, ombitasvir, and ribavirin, OR 24 weeks of sofosbuvir and ribavirin[76]
- HCV genotype 5 or 6: sofosbuvir and ledipasvir[76]

Sofosbuvir with ribavirin and interferon appears to be around 90% effective in those with genotype 1, 4, 5, or 6 disease.[77] Sofosbuvir with just ribavirin appears to be 70 to 95% effective in type 2 and 3 disease but has a higher rate of adverse effects.[77][78] Treatments that contain ledipasvir and sofosbuvir for genotype 1 has success rates of around 93 to 99% but is very expensive.[79] In genotype 6 infection, pegylated interferon and ribavirin is effective in 60 to 90% of cases.[80] There is some tentative data for simeprevir use in type 6 disease as well.[80]

Prior to 2011, treatments consisted of a combination of pegylated interferon alpha and ribavirin for a period of 24 or 48 weeks, depending on HCV genotype.[14] This produces cure rates of between 70 and 80% for genotype 2 and 3, respectively, and 45 to 70% for genotypes 1 and 4.[78] Adverse effects with these treatments were common, with half of people getting flu like symptoms and a third experiencing emotional problems.[14] Treatment during the first six months is more effective than once hepatitis C has become chronic.[27]

Surgery

Cirrhosis due to hepatitis C is a common reason for liver transplantation[27] though the virus usually (80–90% of cases) recurs afterwards.[6][81] Infection of the graft leads to 10–30% of people developing cirrhosis within five years.[82] Treatment with pegylated interferon and ribavirin post transplant decreases the risk of recurrence to 70%.[83]

Alternative medicine

Several alternative therapies are claimed by their proponents to be helpful for hepatitis C including milk thistle, ginseng, and colloidal silver.[84] However, no alternative therapy has been shown to improve outcomes in hepatitis C, and no evidence exists that alternative therapies have any effect on the virus at all.[84][85][86]

Prognosis

The responses to treatment is measured by *sustained viral response* (SVR), defined as the absence of detectable RNA of the hepatitis C virus in blood serum for at least 24 weeks after discontinuing the treatment,[87] and rapid virological response (RVR) defined as undetectable levels achieved within four weeks of treatment. Successful treatment decreases the future risk of hepatocellular carcinoma by 75%.[88]

Disability-adjusted life year for hepatitis C in 2004 per 100,000 inhabitants

- no data
- <10
- 10–15
- 15–20
- 20–25
- 25–30
- 30–35
- 35–40
- 40–45
- 45–50
- 50–75
- 75–100
- >100

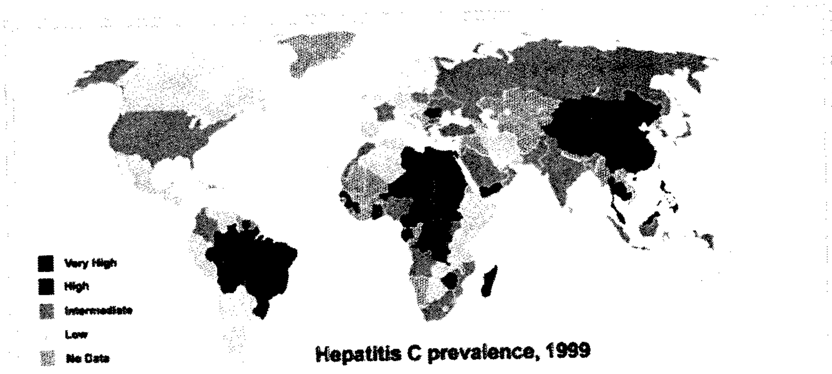
Prior to 2012 sustained response occurs in about 40–50% in people with HCV genotype 1 given 48 weeks of treatment.[6] A sustained response is seen in 70–80% of people with HCV genotypes 2 and 3 with 24 weeks of treatment.[6] A sustained response occurs about 65% in those with genotype 4 after 48 weeks of treatment. The evidence for treatment in genotype 6 disease is sparse and what evidence there is supports 48 weeks of treatment at the same doses used for genotype 1 disease.[89]

Epidemiology

It is estimated that 150–200 million people, or ~3% of the world's population, are living with chronic hepatitis C.[7][8][90] About 3–4 million people are infected per year, and more than 350,000 people die yearly from hepatitis C-related diseases.[90] During 2010 it is estimated that 16,000 people died from acute infections while 196,000 deaths occurred from liver cancer secondary to the infection.[91] Rates have increased substantially in the 20th century due to a combination of intravenous drug abuse and reused but poorly sterilized medical equipment.[24]

Rates are high (>3.5% population infected) in Central and East Asia, North Africa and the Middle East, they are intermediate (1.5%-3.5%) in South and Southeast Asia, sub-Saharan Africa, Andean, Central and Southern Latin America, Caribbean, Oceania, Australasia and Central, Eastern and Western Europe; and they are low (<1.5%) in Asia Pacific, Tropical Latin America and North America.[8]

Among those chronically infected, the risk of cirrhosis after 20 years varies between studies but has been estimated at ~10–15% for men and ~1–5% for women. The reason for this difference is not known. Once cirrhosis is established, the rate of developing hepatocellular carcinoma is ~1–4% per year.[92] Rates of new infections have decreased in the Western world since the 1990s due to improved screening of blood before transfusion.[27]



Prevalence of hepatitis C worldwide in 1999

In the United States, about 2% of people have hepatitis C,[14] with the number of new cases per year stabilized at 17,000 since 2007.[93] The number of deaths from hepatitis C has increased to 15,800 in 2008[94] and by 2007 had overtaken HIV/AIDS as a cause of death in the USA.[95] This mortality rate is expected to increase, as those infected by transfusion before HCV testing become apparent.[96] In Europe the percentage of people with chronic infections has been estimated to be between 0.13 and 3.26%.[97]

In England about 160,000 people are chronically infected.[98] Between 2006 and 2011 28,000 about 3%, received treatment.[98]

The total number of people with this infection is higher in some countries in Africa and Asia.[99] Countries with particularly high rates of infection include Egypt (22%), Pakistan (4.8%) and China (3.2%).[90] It is believed that the high prevalence in Egypt is linked to a now-discontinued mass-treatment campaign for schistosomiasis, using improperly sterilized glass syringes.[24]

History

In the mid-1970s, Harvey J. Alter, Chief of the Infectious Disease Section in the Department of Transfusion Medicine at the National Institutes of Health, and his research team demonstrated how most post-transfusion hepatitis cases were not due to hepatitis A or B viruses. Despite this discovery, international research efforts to identify the virus, initially called *non-A, non-B hepatitis* (NANBH), failed for the next decade. In 1987, Michael Houghton, Qui-Lim Choo, and George Kuo at Chiron Corporation, collaborating with Dr. D.W. Bradley at the Centers for Disease Control and Prevention, used a novel molecular cloning approach to identify the unknown organism and develop a diagnostic test.[100] In 1988, Alter confirmed the virus by verifying its presence in a panel of NANBH specimens. In April 1989, the discovery of HCV was published in two articles in the journal *Science*.[101][102] The discovery led to significant improvements in diagnosis and improved antiviral treatment.[100] In 2000, Drs. Alter and Houghton were honored with the Lasker Award for Clinical Medical Research for "pioneering work leading to the discovery of the virus that causes hepatitis C and the development of screening methods that reduced the risk of blood transfusion-associated hepatitis in the U.S. from 30% in 1970 to virtually zero in 2000."[103]

Chiron filed for several patents on the virus and its diagnosis.[104] A competing patent application by the CDC was dropped in 1990 after Chiron paid $1.9 million to the CDC and $337,500 to Bradley. In 1994, Bradley sued Chiron, seeking to invalidate the patent, have himself included as a coinventor, and receive damages and royalty income. He dropped the suit in 1998 after losing before an appeals court.[105]

Society and culture

World Hepatitis Day, held on July 28, is coordinated by the World Hepatitis Alliance.[106] The economic costs of hepatitis C are significant both to the individual and to society. In the United States the average lifetime cost of the disease was estimated at 33,407 USD in 2003[107] with the cost of a liver transplant as of 2011 costing approximately 200,000 USD.[108] In Canada the cost of a course of antiviral treatment is as high as 30,000 CAD in 2003,[109] while the United States costs are between 9,200 and 17,600 in 1998 USD.[107] In many areas of the world, people are unable to afford treatment with antivirals as they either lack insurance coverage or the insurance they have will not pay for antivirals.[110] In the English National Health Service treatment rates for hepatitis C are higher among wealthier groups per 2010-2012 data.[98]

Research

As of 2011, there are about one hundred medications in development for hepatitis C.[108] These include vaccines to treat hepatitis, immunomodulators, and cyclophilin inhibitors, among others.[111] These potential new treatments have come about due to a better understanding of the hepatitis C virus.[112] The combination of sofosbuvir and velpatasvir in one trial resulted in cure rates of 99%.[113]

Animal models

One barrier to finding treatments for hepatitis C is the lack of a suitable animal model. Despite moderate success, current research highlights the need for pre-clinical testing in mammalian systems such as mouse, particularly for the development of vaccines in poorer communities. Currently, chimpanzees remain the available living system to study, yet their use has ethical concerns and regulatory restrictions. While scientists have made use of human cell culture systems such as hepatocytes, questions have been raised about their accuracy in reflecting the body's response to infection.[114]

One aspect of hepatitis research is to reproduce infections in mammalian models. A strategy is to introduce liver tissues from humans into mice, a technique known as xenotransplantation. This is done by generating chimeric mice, and exposing the mice HCV infection. This engineering process is known to create humanized mice, and provide opportunities to study hepatitis C within the 3D architectural design of the liver and evaluating antiviral compounds.[114] Alternatively, generating inbred mice with susceptibility to HCV would simplify the process of studying mouse models.

Special populations

Children and pregnancy

Compared with adults, infection in children is much less well understood. Worldwide the prevalence of hepatitis C virus infection in pregnant women and children has been estimated to 1–8% and 0.05–5% respectively.[115] The vertical transmission rate has been estimated to be 3–5% and there is a high rate of spontaneous clearance (25–50%) in the children. Higher rates have been reported for both vertical transmission (18%, 6–36% and 41%).[116][117] and prevalence in children (15%).[118]

In developed countries transmission around the time of birth is now the leading cause of HCV infection. In the absence of virus in the mother's blood transmission seems to be rare.[117] Factors associated with an increased rate of infection include membrane rupture of longer than 6 hours before delivery and procedures exposing the infant

to maternal blood.[119] Cesarean sections are not recommended. Breast feeding is considered safe if the nipples are not damaged. Infection around the time of birth in one child does not increase the risk in a subsequent pregnancy. All genotypes appear to have the same risk of transmission.

HCV infection is frequently found in children who have previously been presumed to have non-A, non-B hepatitis and cryptogenic liver disease.[120] The presentation in childhood may be asymptomatic or with elevated liver function tests.[121] While infection is commonly asymptomatic both cirrhosis with liver failure and hepatocellular carcinoma may occur in childhood.

Immunosuppressed

The rate of hepatitis C in immunosuppressed people is higher than the normal population. This is particularly true in those with human immunodeficiency virus infection, recipients of organ transplants and those with hypogammaglobulinemia.[122] Infection in these people is associated with an unusually rapid progression to cirrhosis.

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Further reading

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External links

- Hepatitis C (https://www.dmoz.org/Health/Conditions_and_Diseases/Digestive_Disorders/Liver/Hepatitis/Hepatitis_C) at DMOZ
- Media related to Hepatitis C at Wikimedia Commons
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